

## Claims:

1. A method of identifying a nucleotide change in a TLR4 polynucleotide sequence of an Old World monkey wherein said change may be associated with reduced sensitivity to Gram-negative bacterial infection, comprising the step of:
  - comparing the TLR4 polynucleotide sequence of the Old World monkey with corresponding TLR4 polynucleotide sequence of a human to identify a polynucleotide change in said Old World monkey's TLR4 sequence that is evolutionarily meaningful, whereby said evolutionarily meaningful change may be associated with reduced sensitivity to Gram-negative bacterial infection.
2. The method of claim 1 wherein the Old World monkey is selected from the group consisting of rhesus monkey and baboon.
3. The method of claim 2 wherein the evolutionarily meaningful change is from Asp299 in the human to Asn299 in the rhesus monkey or baboon.
4. The method of claim 3, wherein the evolutionarily meaningful change is associated with the reduced sensitivity to Gram-negative bacterial infection by the step comprising:
  - analyzing the functional effect of the Asp299Asn change in a model system.
5. The method of claim 4, wherein said model system is *in vivo*, *ex vivo* or *in vitro*.
6. A method of identifying a therapeutic agent that reduces sensitivity to Gram-negative bacterial infection, comprising:
  - (a) contacting candidate agents with human TLR4 polypeptide; and
  - (b) identifying a therapeutic agent that interacts with the TLR4 polypeptide to substantially reduce sensitivity to Gram-negative bacterial infection.
7. The method of claim 6 wherein said interaction with TLR4 polypeptide occurs at Asp299.

8. The method of claim 6, wherein said substantial reduction in sensitivity to Gram-negative bacterial infection is determined by an indicator selected from the group consisting of:

- 5 (a) elimination or substantial reduction in host systemic inflammatory response to LPS in a human, non-human primate, or suitable animal model; and
- (b) elimination or reduced severity of central nervous system dysfunction, adult respiratory distress syndrome, liver failure, acute renal failure, and/or disseminated intravascular coagulation in a human, non-human primate, or suitable animal model.

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9. A method for treating sepsis, severe sepsis or septic shock in a primate, comprising:

administering to a primate in need thereof an effective dose of a therapeutic agent identified according to the method of claim 6.

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10. A method for treating asthma in a primate, comprising:

administering to a primate in need thereof an effective dose of a therapeutic agent identified according to the method of claim 6.

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11. A therapeutic agent identified according to the method of claim 6.

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12. A composition comprising a polynucleotide selected from the group consisting of chimpanzee *TLR4* polynucleotide (SEQ. ID. NO. 1), gorilla *TLR4* polynucleotide (SEQ. ID. NO. 4), gibbon *TLR4* polynucleotide (SEQ. ID. NO. 7), rhesus monkey *TLR4* polynucleotide (SEQ. ID. NO. 10), capuchin *TLR4* polynucleotide (SEQ. ID. NO. 13), squirrel monkey *TLR4* polynucleotide (SEQ. ID. NO. 16), and baboon *TLR4* polynucleotide (SEQ. ID. NO. 19).

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13. A composition comprising a polypeptide selected from the group consisting of chimpanzee *TLR4* polypeptide (SEQ. ID. NO. 3), gorilla *TLR4* polypeptide (SEQ. ID. NO. 8), gibbon *TLR4* polypeptide (SEQ. ID. NO. 9), rhesus monkey *TLR4* polypeptide (SEQ. ID. NO. 12), capuchin *TLR4* polypeptide (SEQ. ID. NO. 15), squirrel monkey *TLR4* polypeptide (SEQ. ID. NO. 18), and baboon *TLR4* polypeptide (SEQ. ID. NO. 21).